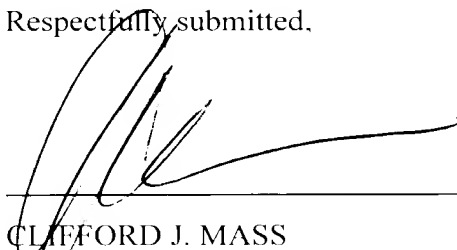


### REMARKS

The above amendatory action to the claims is taken solely for the purpose of avoiding claim fees that would otherwise accrue due to the presence of multiple dependent claims, with the exception that the Accession Nos. in claims 1, 21, 22 and 24 have been amended based on the disclosure in the Abstract of International Publication WO 99/66047 (PCT/SG98/00045) to correct an inadvertant clerical error.

The amendatory action to the specification is taken to comply with the applicable sequence listing requirements. A computer readable copy of the Sequence Listing and the requisite statement are submitted herewith.

Respectfully submitted,



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1. (Amended) An isolated strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine) and deposited under Accession Nos. P9712150 4, P9712150 5 and P9712150 6 with the European Collection of Cell Culture on 15<sup>th</sup> December 1997.
  
14. (Amended) The vector of claim 12 mutis, wherein the vector comprises viral DNA.
  
21. (Amended) A purified polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus deposited under Accession Nos. P9712150 4, P9712150 5 and P9712150 6 with the European Collection of Cell Culture on 15<sup>th</sup> December 1997, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine rather than a glycine.
  
22. (Amended) A purified polypeptide obtained from a method which comprises:
  - (a) introducing a vector comprising an isolated nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus deposited under Accession Nos. P9712150 4, P9712150 5 and P9712150 6 with the European Collection of Cell Culture on 15<sup>th</sup> December 1997, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine rather than a glycine and operatively linked to a promoter of RNA transcription into a suitable host cell;
  - (b) culturing the resulting host cell so as to produce the polypeptide;
  - (c) recovering the polypeptide produced in step (b); and
  - (d) purifying the polypeptide so recovered.
  
24. (Amended) A purified peptide obtained from a method which comprises:

- (a) introducing a vector comprising an isolated nucleic acid encoding a peptide which comprises at least a portion of a mutant major surface antigen of a strain of hepatitis B virus deposited under Accession Nos. P9712150 4, P9712150 5 and P9712150 6 with the European Collection of Cell Culture on 15<sup>th</sup> December 1997 wherein the peptide is encoded by a nucleic acid molecule comprising nucleotides 527 through 595 of SEQ. I.D. No. 1 into a suitable host cell;
- (b) culturing the resulting host cell so as to produce the polypeptide;
- (c) recovering the polypeptide produced in step (b); and
- (d) purifying the polypeptide so recovered.

33. (Amended) The antibodies obtained in claim 27.

37. (Amended) A method for use of a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine for determining whether a subject is infected with a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine), wherein such method comprises

- (a) obtaining an appropriate nucleic acid sample from the subject; and
- (b) determining whether the nucleic acid sample from step (a) is, or is derived from, a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine.

38. (Amended) A method for use of a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a

major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine for determining whether a subject is infected with a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine), wherein such method comprises

- (a) obtaining an appropriate nucleic acid sample from the subject; and
- (b) determining whether the nucleic acid sample from step (a) is, or is derived from, a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, wherein the nucleic acid sample in step (a) comprises mRNA corresponding to the transcript of DNA encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, and wherein the determining of step (b) comprises:
  - (i) contacting the mRNA with the oligonucleotide of claim 25 under conditions permitting binding of the mRNA to the oligonucleotide so as to form a complex;
  - (ii) isolating the complex so formed; and
  - (iii) identifying the mRNA in the isolated complex so as to thereby determine whether the mRNA is, or is derived from, a nucleic acid which encodes the polypeptide.

39. (Amended) The method of claim 37, wherein the nucleic acid sample in step

- (a) comprises mRNA corresponding to the transcript of DNA encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the

amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, and wherein the determining of step (b) comprises:

- (i) translating the mRNA under suitable conditions to obtain an amino acid sequence; and
- (ii) comparing the amino acid sequence of step (i) with the amino acid sequence encoded by the an isolated nucleic acid of claim 1 encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine rather than a glycine, wherein the polypeptide has an amino acid sequence substantially the same as amino acid residues 174 through 400 of the amino acid sequence designated SEQ. I.D. No. 3 so as to determine whether the nucleic acid sample is, or is derived from, a nucleic acid which encodes the polypeptide.

40. (Amended) The method of claim 37, wherein the determining of step (b) comprises:

- (i) amplifying the nucleic acid present in the sample of step (a); and
- (ii) detecting the presence of polypeptide in the resulting amplified nucleic acid.

41. (Amended) A method of use of antibodies capable of detecting a polypeptide which is a mutant major surface antigen of a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine) for determining whether a subject is infected with a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine), wherein such method comprises:

- (a) obtaining an appropriate sample from the subject; and
- (b) determining whether the sample from step (a) is, or is derived from, a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, by contacting the sample under appropriate conditions to bind to the antibodies of claim 35 so as to determine whether a subject is infected.

42. (Amended) The method of claim 37, 38 or 4 wherein the isolated nucleic acid, oligonucleotide, or antibody is labeled with a detectable marker.

43. (Amended) The method of claim 42, wherein the detectable marker is a radioactive isotope, a fluorophor, or an enzyme.

44. (Amended) The method of claim 37, wherein the sample comprises blood, tissue, or sera.

51. (Amended) A method comprising administering the composition of claim 47 for treating a subject infected with a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine).

52. (Amended) A method comprising administering the composition of claim 49 for treating a subject infected with a strain of hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine).

53. (Amended) A method comprising administering the composition of claim 47 for preventing infection by a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine) in a subject.

54. (Amended) A method comprising administering the composition of claim 50 for preventing infection with a strain of Hepatitis B virus designated Human Hepatitis B Virus Surface Antigen-'S'-145 Singapore Strain (Glycine to Arginine) in a subject.

57. (Amended) A method for use of an antibody that recognizes a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus for determining whether the subject has a predisposition for hepatocellular carcinoma, wherein ~~said method~~ said method comprises:

- (a) obtaining an appropriate nucleic acid sample from the subject; and
- (b) determining whether the nucleic acid sample from step (a) is, or is derived from, a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, by contacting the sample under appropriate conditions to bind to the antibodies of claim 35 so as to determine whether the subject has a predisposition for hepatocellular carcinoma.

58. (Amended) The method of claim 57, wherein the nucleic acid sample in step (a) comprises mRNA encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, and wherein the determining of step (b) comprises:

- (i) contacting the mRNA with ~~the~~ an oligonucleotide of ~~length of at least 15 nucleotides capable of specifically hybridizing with a unique sequence of nucleotides within a nucleic acid which encodes a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major~~

surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine rather than a glycine, without hybridizing to any sequence of nucleotides within a nucleic acid which encodes the major surface antigen of a wildtype hepatitis B virus under conditions permitting binding of the mRNA to the oligonucleotide so as to form a complex;

- (ii) isolating the complex so formed; and
- (iii) identifying the mRNA in the isolated complex so as to thereby determined whether the mRNA is, or is derived from, a nucleic acid which encodes the polypeptide.

59. (Amended) The method of claim 57, wherein the nucleic acid sample in step (a) comprises mRNA encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, and wherein the determining of step (b) comprises:

- (i) translating the mRNA under suitable conditions to obtain an amino acid sequence; and
- (ii) comparing the amino acid sequence of step (i) with the amino acid sequence encoded by the an isolated nucleic acid which encodes a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine rather than a glycine, wherein the polypeptide has an amino acid sequence substantially the same as amino acid residues 174 through 400 of the amino acid sequence designated SEQ. I.D. No. 3 so as to determine whether the nucleic acid sample is, or is derived from, a nucleic acid which encodes the polypeptide.



61. (Amended) A method for use of an antibody that recognizes a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus for determining whether the subject has a predisposition for hepatocellular carcinoma, wherein said method comprises:

- (a) obtaining an appropriate sample from the subject; and
- (b) determining whether the sample from step (a) is, or is derived from, a nucleic acid encoding a polypeptide which is a mutant major surface antigen of a strain of hepatitis B virus, such polypeptide having an amino acid sequence which differs from the amino acid sequence of a major surface antigen of a wildtype hepatitis B virus in that the amino acid at position number 145 of such polypeptide is an arginine, rather than a glycine, by contacting the sample under appropriate conditions to bind to the antibodies of claim 36 so as to determine whether the subject has a predisposition for hepatocellular carcinoma.

62. (Amended) The method of claim 58, wherein the oligonucleotide or antibody is labeled with a detectable marker.

69. (Amended) A method comprising administering the composition of claim 47 as a medicament for treating hepatocellular carcinoma.

70. (Amended) A method comprising administering the composition of claim 67 as a medicament for treating hepatocellular carcinoma.

71. (Amended) A method comprising administering the composition of claim 47 as a medicament for preventing hepatocellular carcinoma.

72. (Amended) A method comprising administering the composition of claim 67 as a medicament for preventing hepatocellular carcinoma.